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Intensive review on pharmacology and therapy of gout

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Abstract

Out is a metabolic disorder characterised by precipitation of uric acid crystals especially in smaller bones of feet (commonest is metatarso - phalangeal joint in great toe), joints, kidney, subcutaneous tissue. The major symptoms of gout include severe attacks of pain, lingering discomfort, inflammation, redness and limited range of movement. Gout is caused due to deposition of uric acid which is a metabolic product of purines which naturally occurs in our body. Normally uric acid dissolves in our body but when the concentration increases above 6mg/dl because of improper functioning of kidney or over production of it by our body causes its deposition in the joints. People usually experience gout signs and symptoms again and again but medications can help prevent the gout attacks. If its left untreated it may cause erosion, stiffness and destruction of the joint. Therefore, there is an urgent need to explore effective diagnostic approaches to catch and better treat the disease before it worsens. Usually joint fluid test, blood test, X-ray imaging, ultra sound, dual energy CT scan are used for diagnosis. Joint fluid and blood test help in finding the uric acid crystals under microscope whereas the X-ray ultra sound examine soft tissues and bone. Gout can be controlled by medication by either reducing pain on attack or reducing the uric acid build up. NSAIDS are given for reducing the pain and inflammation and if NSAIDS are taken in 1st 24hrs then it helps in shortening the attack. In sever cases uricosuric drugs or uric acid synthesis inhibitors are used to prevent the uric acid production.

Keywords: Uric acid crystals, Metatarso-phalangeal joint, Purines, Ultra sound, Joint fluid test, CT scan, NSAIDS, Uricosuric drugs.

INTRODUCTION

Gout is a metabolic disorder characterised by hyperuricemia (high levels of uric acid). It is caused by uric acid deposition/precipitation in the joint spaces, kidney, and subcutaneous tissue. It often starts from the big toe i.e. metatarso-phalangeal joint and it may also form lumps under skin and in kidney. Uric acid concentration increases either by improper clearance by kidney or excess production by our body. Uric acid is a metabolic by product produced from purines with is present in our DNA. It usually occurs in middle aged people and most common in males when compared to females. It's because in women before menopause the oestrogen which is produced blocks the anion exchange transporter in the kidney causing more uric acid to be excreted in urine and thus lowering the uric acid levels in blood. But the post-menopausal women are also at the same risk like that of male. Each year there are more than 3.9 million people approaching due to gout and this majority of cases can be managed by primary care.

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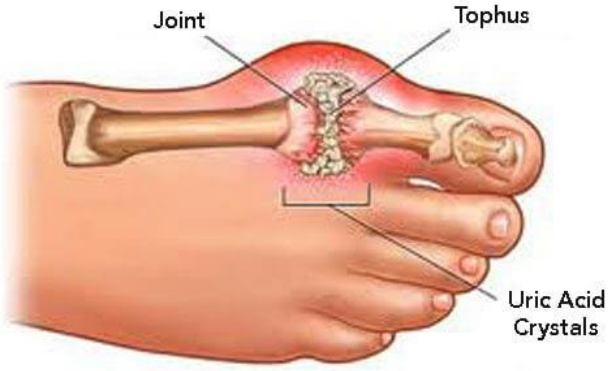
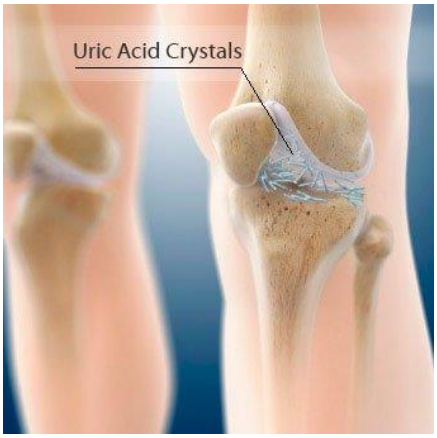
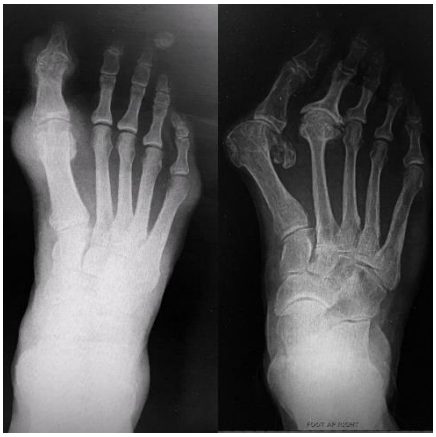




Based on the type of deposition they can be classified into [6]

Tophaceous gout: - it occurs when gout attacks become more frequent at short intervals without resolving inflammation during this period. Yellow or white lumps of uric acid are found in Tophaceous gout patients. Very rarely these lumps are also spotted around spinal cord and kidney. At times there are instances of these tophi breaking through the skin resembling crab eyes. Usually these tophi are painless but they may cause discomfort and stiffness in the effected area. If left untreated they may cause wear and tear of cartilage and bones and ultimately destroys the joint.

Pseudogout: - it is a type of arthritis in which one or more joints are affected with excruciating swelling due to deposition of calcium pyrophosphate and episodes may last from days to weeks. Major joints that get effected are knees, wrists, shoulders, and hips. Pseudogout is clearly related to aging and it is associated with degenerative arthritis. This is particularly common in elderly patients, hospitalised patients and in patients recovering from operations which is mostly caused by dehydration. It can also be caused by hormonal effects on calcium metabolism from hyperparathyroidism.



Stages of gout

There are several stages of gout

Asymptomatic hyperuricemia – At this stage there are no visible symptoms but the uric acid levels are high in blood and the crystals start forming at joint spaces. Although most patients will have high levels of uric acid in their blood for years before having their first gout attack and there is no current recommendation for treatment during this period. This is termed as asymptomatic hyperuricemia.

Acute gout: - This happens when something (such as a night of alcohol drinking, intake of high purine diet, etc) causes increase in uric acid levels or jostles the crystals that have been previously formed at a joint trigger the attack. The resulting inflammation and pain usually strikes at night and

intensifies in the next 8-12 hours. The symptoms are likely to reduce in a week or 10 days.

Interval gout- This is the time between the attacks or flares. During this period the patient does not experience pain but that doesn't mean that gout is gone. This is the time where patient must become more cautious and begin to manage gout via lifestyle changes and medication to prevent future attacks of gout and chronic gout.

Chronic gout- It develops in people with gout and hyperuricemia over many years. Attacks become more frequent and pain persists. Chronic gout can be a relapsing problem with several attacks that occur in short durations and without complete resolution of inflammation between attacks. This can cause significant joint destruction and deformity.

Symptoms and signs [9]

- Intense pain in the affected area
- Lessened flexibility and limited joint moment
- Extreme tenderness of the joint even to lightest touch
- Swelling, inflammation, and a feeling that the joint is hot
- In extreme cases effected by chills and fever
- Red or purple skin around the affected joint

Risk factors

- Obesity or over weight
- Family history of gout
- Excess intake of alcohol- excess alcohol intake causes dehydration which causes improper clearance of uric acid
- Diet containing high amount of purines
- Lead exposure- lead injures the kidney and impairs their ability to clear uric acid from blood
- Genetic defect- Some people overproduce uric acid due to a genetic defect in an enzyme in the purine breakdown pathway which leads to overactivity of this pathway. Since cells contain DNA, and DNA contains purines, anything that increases the breakdown of cells in the body can lead to more uric acid and gout.
- Dehydration

Health related risk factors

- Renal insuffiency- kidneys excrete uric acid predisposing CKD patients to hyperuricemia **[5]**
- High blood pressure- High blood pressure is another major risk factor for gout. It gets complicated, though, because the diuretics taken to lower high blood pressure increase uric acid levels, so the treatment as well as the disease are associated with the disease. **[4]**
- Kelley-Seegmiller syndrome or Lesch-Nyhan syndrome, two rare conditions in which your body doesn't have enough of the enzyme that helps control uric acid levels.
- Insulin resistance-Type 2 diabetes happens when your body doesn't use insulin well and sugar stays in the blood instead of moving into cells. This is called insulin resistance. Higher levels of insulin circulating throughout the body inhibit uric acid elimination by the kidneys.
- High cholesterol-high cholesterol is independently and directly related to high uric acid in the blood, although the causal relationship between the two is still unknown to this day.
- Hypothyroidism-hyperthyroidism can cause hyperuricemia through the increase of purine nucleotide turn over and the decrease of renal urate excretion.
- Cancer-if a patient is receiving chemotherapy for a tumour, as the treatment kills the tumour cells a gout attack can develop as a result of the breakdown of the purines from those cells. Conditions that make your cells reproduce and shed more quickly than usual, such as psoriasis, haemolytic anaemia, and some cancers.

Drug related risk factors

- Diuretics – Diuretics increase the body's water and sodium excretion. This allows the blood vessel walls to relax, alleviating high blood pressure. However, this can also cause an increase in the blood uric acid concentration.
- Niacin- Your kidneys, while working to rid your body of niacin, may fail to excrete uric acid, leading to gout.
- Aspirin with salicylate- aspirin or other salicylates can increase plasma uric acid levels and increase the risk of gout. Aspirin and other salicylates can also interfere with the

action of uricosuric drugs prescribed for the treatment of gout.

- Cyclosporin- hyperuricemia is a common complication of cyclosporine therapy and is caused by decreased renal urate clearance. [7]
- Levodopa-it's found that a 440 mg/kg dose of L-dopa given by stomach tube results in a 30% decrease in the renal tubular excretory transport of uric acid. L-Dopa infused along with uric acid into the renal portal circulation also decreases the excretory transport of uric acid. **[8]**

Diagnosis [6]

There are many diagnostic tests to identify gout such as: -

- **Synovial fluid examination**- this involves collection of sample from the affected joint through a needle and examining of it under a microscope for urate crystals. This test can conform the diagnosis but at times it becomes difficult to collect sample from a small joint such as the big toe. A fine needle inserted into tophus under your skin can also be used to identify the urate crystals
- **Blood test**- this helps us to measure the amount of uric acid present in our blood. The critical serum level of uric acid in blood is 6mg/dl for men and elderly women. A raised level of uric acid levels in blood strongly supports the diagnosis of gout but can't confirm it, as not everyone with high levels of uric acid suffers from gout.
- **X-ray**- x-rays are rarely suggested as they do not confirm it as gout as they are usually normal in initial stages.
- **Ultrasound**- Musculoskeletal ultrasound can detect urate crystals in a joint or in a tophus and hence the most widely used technique for diagnosis of gout.
- **Dual energy CT scan**- This type of imaging can detect the presence of urate crystals in a joint, even when it is not acutely inflamed. This test is not used routinely in clinical practice due to the expense and is not widely available.

Treatment

Goals of treatment- [11]

- terminate the acute attacks
- prevent recurrent attacks
- prevent complications associated with chronic deposition of urate crystals in tissue
- to ward off joint damage
- to protect against kidney dysfunction

Non-pharmacological treatment

Diet and life style changes- [10]

- Low-fat dairy products
- Avoid crash diets, since fast or extreme weight loss can increase the amount of uric acid in the body. High-protein diets may be a problem for people with gout because of the high-purine foods on many of the diets, especially red meat and shellfish.
- limit alcohol intake-Only a moderate amount of wine up to two 5-ounce servings per day [about 300 mL per day] may be acceptable, unless the individual patient has found that this increases their risk of a gout attack as heavy alcohol drinking raises the uric acid level and increases the risk of gout through adenine nucleotide degradation and lactate production.
- Coffee-may decrease serum uric acid levels
- Vitamin C (a mild urate-lowering effect)- The risk of gout appears to be lower in men taking daily vitamins. Vitamin C may be a useful supplement in the 500 to 1000 mg per day range.
- Know Your Uric Acid Level – Uric acid levels should be checked at least twice per year. The goal should be to have your uric acid level below 6.0 mg/dL.
- Maintain a Healthy Body Weight – An obese person is four times more likely to develop gout than someone with ideal body weight
- Exercise Regularly
- Stay Hydrated - Some experts believe that drinking water can help remove uric acid from the bloodstream. Avoid sports drinks sweetened with high-fructose corn syrup
- Rest and topical ice application are important adjuncts to managing acute gout.

Pharmacological treatment

1. **NSAIDS [1, 2]**

   Most patients may be treated successfully with nonsteroidal anti-inflammatory drugs. They are quite effective in terminating the attack, but may take 12-24 hrs. after the attack is over they may be continued at lower doses for 3-4 weeks. they are not recommended for long

term usage due to their toxic effects. Generally used NSAIDS are indomethacin (300-500mg twice daily), naproxen (750mg followed by 250mg for every 8hrs until attack subsides), sulindac (150-200mg twice daily for 7-10 days), ibuprofen (400-800mg 3-4 times daily), ketoprofen (50-75mg 3-4 times daily), celecoxib (800mg followed by 400mg on 1st day, 400mg twice daily for 1 week). **[2]**

Adverse effect- GI tract disturbances, kidney problems, cardiovascular problems and CNS problems

2. **Corticosteroids**

Corticosteroids have efficacy equivalent to NSAIDS. Intraarticular injection of soluble steroid supresses the symptoms. Systemic therapy is necessary if an attack is polyarticular. It is usually used in refractory cases and those not tolerating NSAIDS/ colchicine. Commonly used corticosteroids are prednisone (0.5mg/kg daily for 2-3 days followed by tapering for 7-10 days), methyl prednisolone (24mg on 1st day and dose reduced by 4mg daily), ACTH (40-80 usp units given IM for every 6-8 hrs for 2-3 days and discontinued)

Adverse effect- GI problems, bleeding disorders, cardio vascular diseases, psychiatric disorders, long term usage causes – osteoporosis, cataract, muscle deconditioning.

3. **Colchicine**

It's an alkaloid from colchicum autumnale. it is nor analgesic nor anti-inflammatory but is highly effective in specifically supressing the gouty inflammation. It does not inhibit the synthesis nor promote excretion of uric acid and thus it has no effect on blood levels of uric acid. It shows its effect by inhibiting the release of chemotactic factors.

Dose – 1.2mg initially followed by 0.6mg 1hr later

Adverse effect- nausea, vomiting, diarrhoea, neutropenia, axonal neuromyopathy

4. **Urate-Lowering Therapy**- It can be started during an acute attack if anti-inflammatory prophylaxis has been initiated. the goal of this therapy is to achieve and maintain serum uric acid levels less than 6mg/dl. serum urate can be reduced either by decreasing synthesis of uric acid or by increasing renal excretion of uric acid.

a) **Xanthine oxidase inhibitors**- act by reducing the synthesis of uric acid by impairing the conversion of hypoxanthine to xanthine and xanthine to uric acid and hence used as 1st line agent. **[1, 2]**

- **Allopurino**l- it's a hypoxanthine analogue which is synthesised as purine antimetabolite which acts as inhibitor of xanthine oxidase, the enzyme responsible for uric acid synthesis.it lowers uric acid levels in dose dependent manner. **[1]**

  Dose- 100mg daily dose as starting dose which is gradually increased every 2-5 weeks up to a maximum of 800mg/day until the serum rate target is achieved. (Patients with CKD should start with 50mg as starting dose) **[2]**

  Adverse effect- skin rash, leukopenia, GI problems, head ache, urticaria, or few hypersensitivity reactions characterised by fever, dermatitis, eosinophilia, renal and hepatic dysfunction.

- **Febuxostat**-it is used as an alternative drug for treating symptomatic gout only in patients intolerant to allopurinol or in those with some contraindications.

  Dose- 40mg/day is taken as a starting dose and increase dose to 80mg/day for patients who do not achieve target serum uric acid concentration after 2 weeks of therapy.

  Adverse effect- nausea, arthralgias, minor hepatic transaminase elevations

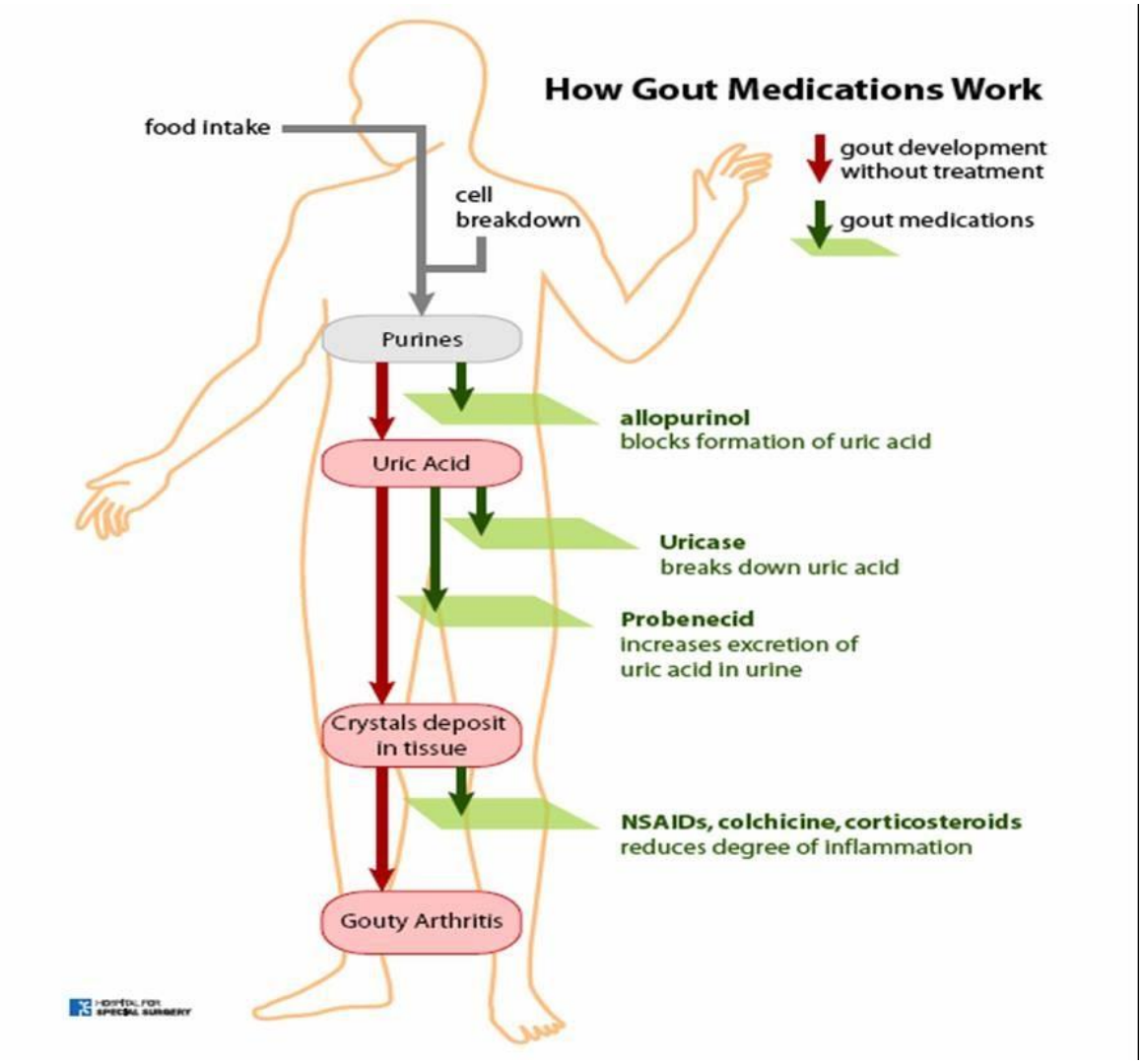
b) **Uricosurics**- these act by increasing the renal excretion of uric acid. **[1, 2]**

- **Probenecid**-increases renal clearance of uric acid by inhibiting the post secretory renal proximal tubular reabsorption of uric acid.

  Dose-250mg twice daily for 1-2 weeks, 500mg twice daily for 2 weeks, it can be increased on weekly basis until satisfactory result is obtained but dose must not exceed 2g/day.

  Adverse effect- GI irritation, rash, dyspepsia, hypersensitivity reactions. **[2, 3]**

  In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric is suggested.



Complications of gout

- If gout is left untreated then people may suffer numerous gout attacks over years and that may lead to irreversible and permanent joint damage. Eventually the effected joints can come out of alignment and can become completely immobile or disabled.
- Gout after several years of development if not properly taken care of leads to development of tophi i.e. uric acid deposition in soft tissues especially around the joints.
- People with gout are at high risk of developing kidney stones. The kidney stones are composed of uric acid crystals and calcium crystals that are part of gout. The crystals get collected in the urinary tract and tend to form stone. If the stone is large enough it may block one of the ureters. **[5]**
- Heart diseases are next common complication of gout since gout is associated with increased levels of unhealthy cholesterol and lipids.
- Development of cataract is being rarely seen in gout patients
- Accumulation of uric acid crystals in lungs are also seen in rare cases
- It also effects the psychological condition of the patient causing depression and anxiety.

Conclusion

Gout is not a disease which can't be cured. It can be cured and we can also prevent further complications easily when the patient is diagnosed based on signs and symptoms and diagnostic values. Proper medication and lifestyle changes are also necessary in controlling the disease from acute attacks to chronic gout attacks.

Reference

[1]. K.D Tripathi. Essentials of medical pharmacology, 7.th edition
[2]. Barbara G. Wells, Joseph T. Dipiro, Terry L. schwinghammer, Cecily V. Dipiro pharmacotherapy, 9th edition
[3]. Karen Whalen, Richard Finkel, Thomas A. Panavelil Lippincott illustrated reviews: pharmacology, 6th edition
[4]. Baylor college of medicine- "high levels of uric acid may be associated with high blood pressure"-science daily 27, 2008
[5]. Mary Rogers Sorey ACNP-BC- gout management in patients with CKD – clinical feature- 2013
[6]. Dr Robert Shmerling – all about gout – Harvard health letter/ the health letter- 2010
[7]. Lintly, RocherLL, McQuillan MA- cyclosporine – induced hyperuricemia and gout – n. Engl J Med – 321(5), 1989, 287-92
[8]. Bierer DW, Quebbemann AJ- effect of L-dopa on renal handling of uric acid – J pharmacol Exp Ther – 223(1), 1982, 55-9
[9]. Kevin K Anbari MD, MBA – gout symptoms
[10]. Catherine Burt Driver, MD, FACP- Guidelines for management of gouty arthritis – published by American college of rheumatology
[11]. J Edwin Seegmiller MD – goals in gout – post graduate medicine –45(1), 1969- rheumatic disease

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